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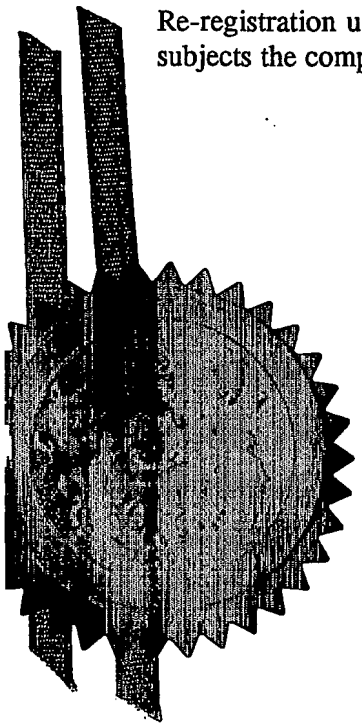

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Patents ADP number *(if you know it)*

06008031002

If the applicant is a corporate body, give the country/state of its incorporation

UK (SCOTLAND)

4. Title of the invention

ANTIOXIDANT WOUND DRESSING MATERIALS

5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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ANTIOXIDANT WOUND DRESSING MATERIALS

The present invention relates to antioxidant wound dressing materials, processes suitable for the preparation of such materials, and to the use of such wound dressing materials.

Concentrations of reactive oxygen species such as hydroxyl radicals (·OH), singlet oxygen ($^1O_2$), hydroperoxyl radicals (·OOH), superoxideradical anions ($\cdot O_2^-$), and hydrogen peroxide (H_2O_2) can rise in damaged tissues, producing a condition known as oxidative stress. The presence of a low level of reactive oxygen species may be advantageous in the early stages of wound healing by both attracting and activating macrophages which engulf and kill bacteria and release cytokines and growth factors. However, prolonged and more severe oxidative stress may delay healing because it will produce chronic inflammation, divert available energy supply towards antioxidant defence at the expense of tissue reconstruction, and increase levels of matrix metalloproteinases which cause tissue breakdown. In more severe cases, elevated levels of reactive oxygen species can give rise to hydrogen peroxide-induced senescence or apoptosis (that is, programmed cell death) or tissue necrosis (that is, uncontrolled cell death and therefore permanent tissue damage).

Under mild oxidative stress, it is thought that hydrogen peroxide (H_2O_2) is the dominant species present, being formed rapidly from superoxide by the enzyme superoxide dismutase. This enzyme-mediated dismutation reaction also minimises the production of singlet oxygen that can arise when superoxide is produced too rapidly and therefore has the opportunity to dismutate spontaneously without enzyme assistance. Rapid enzyme-mediated dismutation of superoxide also minimises levels of hydroperoxyl radical, the unionised form of superoxide. Levels of hydrogen peroxide are in turn kept low by the actions of catalase and glutathione peroxidase. Thus, under mild oxidative stress conditions when hydrogen peroxide levels are slightly raised (around 10^{-8} to 10^{-4} molar), it has been found that the rate of cell proliferation in fibroblast cultures is stimulated.

Accordingly, the healing of chronic wounds may be assisted by the use of antioxidant wound dressings that react specifically with excess reactive oxygen species such as those listed above and hence reduce the level of oxidative stress.

US-A-5667501 describes compositions comprising chemically modified polymers grafted with chemical groups that confer antioxidant activity as measured by a diphenylpicrylhydrazyl (DPPH) test and that also generate low levels of hydrogen peroxide by reaction with molecular oxygen in the wound bed to stimulate macrophage activity and fibroblast proliferation. The compositions may be used to promote the healing of chronic wounds. Preferably, the polymer is a polymer bearing hydroxyl, carbonyl or amide functional groups, or a polysaccharide bearing hydroxyl functional groups, said functional groups having been converted to derivatives that are persistent free radicals or precursors of persistent free radicals, that is to say they are free radical scavenging antioxidant groups.

US-A-5612321 describes compositions comprising polysaccharides grafted with antioxidants on at least one hydroxyl group of the polysaccharide. The compositions may be used inter alia to promote the healing of chronic wounds. Preferably, the polysaccharide is hyaluronic acid and the antioxidant group comprises a phenol group.

The above antioxidant wound dressing materials are made by multi-step chemical reactions to achieve covalent bonding of antioxidant moieties, such as hydroquinones or benzimidazole derivatives, to the polymeric substrate materials. A need remains for a more simple and inexpensive route to antioxidant wound dressing materials.

In a first aspect, the present invention provides a wound dressing material comprising a solid bioabsorbable substrate dyed with an antioxidant dyestuff.

It has been found that bioabsorbable substrate materials such as oxidized regenerated cellulose have excellent avidity for antioxidant dyes such as aniline and acridine dyes. This enables controlled amounts of the dyes to be fixed onto

the substrate materials in a simple and inexpensive dyeing step. It has further been found that the resulting dyed materials retain the antioxidant properties of the dyestuff, thereby making them excellent candidates for the treatment of chronic wounds and other wounds characterised by elevated levels of oxygen free radicals. The materials also have useful antimicrobial properties, in particular against gram-positive and sometimes also gram-negative bacteria.

The term "bioabsorbable substrate material" refers to a solid material that is fully degraded and absorbed *in vivo* in the mammalian body. The term therefore does not encompass cellulose or conventional textile materials. The substrate material is usually not water soluble, but it may be water swellable. In certain embodiments, the substrate comprises (and may consist essentially of) a solid bioabsorbable material selected from the group consisting of collagens, bioabsorbable cellulose derivatives such as oxidized celluloses, galactomannans such as guar/borate, glycosaminoglycans such as cross-linked hyaluronates, polylactides/polyglycolides, polyhydroxybutyrates, and mixtures thereof.

In certain embodiments the substrate comprises (and may consist essentially of) a solid bioabsorbable material selected from the group consisting of collagens, chitosans, oxidized regenerated celluloses, and mixtures thereof.

Oxidized cellulose is produced by the oxidation of cellulose, for example with dinitrogen tetroxide. This process converts primary alcohol groups on the saccharide residues to carboxylic acid group, forming uronic acid residues within the cellulose chain. The oxidation does not proceed with complete selectivity, and as a result hydroxyl groups on carbons 2 and 3 are occasionally converted to the keto form. These ketone units introduce an alkali labile link, which at pH7 or higher initiates the decomposition of the polymer via formation of a lactone and sugar ring cleavage. As a result, oxidized cellulose is biodegradable and bioabsorbable under physiological conditions.

The preferred oxidized cellulose for practical applications is oxidized regenerated cellulose (ORC) prepared by oxidation of a regenerated cellulose, such as rayon.

It has been known for some time that ORC has haemostatic properties, and that application of ORC fabric can be used to reduce the extent of post-surgical adhesions in abdominal surgery.

The oxidized regenerated cellulose (ORC) can be obtained by the process described in US Patent No. 3122479, the entire content of which is incorporated herein by reference. This material offers numerous advantages including the features that it is biocompatible, biodegradable, non-immunogenic and readily commercially available. ORC is available with varying degrees of oxidation and hence rates of degradation. The ORC may be used in the form of insoluble fibers, including woven, non-woven and knitted fabrics. In other embodiments, the ORC is in the form of water-soluble low molecular weight fragments obtained by alkali hydrolysis of ORC.

In preferred embodiments, the oxidized cellulose is in the form of particles, such as fiber particles or powder particles, preferably dispersed in a suitable solid or semisolid topical medicament vehicle. In particular, the materials preferably contain ORC fibers, wherein a volume fraction of at least 80% of the fibers have lengths in the range of 20μm to 1000μm. Such a size distribution can be achieved, for example, by milling an ORC cloth, followed by sieving the milled powder to remove fibers outside the range. Preferably, the average (mean by volume) length of the ORC fibers is in the range 250μm to 450μm. The selection of ORC fiber lengths in this range results in easy mixing of the ORC and chitosan and highly homogeneous products. The ORC is more thoroughly complexed with the chitosan, which results in enhanced therapeutic properties of the sponge.

Preferably, the oxidised cellulose has an average molecular weight greater than 50,000. Such oxidised cellulose is substantially insoluble in wound fluids, but will undergo very gradual breakdown into bioresorbable fragments at physiological pH. Preferably, the oxidized cellulose is not neutralized. However, the present invention encompasses the use of partially or completely neutralised materials as described in EP-A-0437095 for the preparation of medicaments for the treatment of chronic wounds as hereinbefore defined.

Chitin is a natural biopolymer composed of N-acetyl-D-glucosamine units. Chitin may be extracted from the outer shell of shrimps and crabs in known fashion. The chitin is then partially deacetylated, for example by treatment with 5M-15M NaOH, to produce chitosan. Complete deacetylation of the chitin is not a practical possibility, but preferably the chitosan is at least 50% deacetylated, more preferably at least 75% deacetylated. Chitosan has been employed for wound treatment in various physical forms, e.g. as a solution/gel; film/membrane; sponge; powder or fiber. Chitosan in the free base form is swellable but not substantially soluble in water at near-neutral pH, but soluble in acids due to the presence of ammonium groups on the chitosan chain. The solubility of the chitosan may be reduced by cross-linking, for example with epichlorhydrin. Typically, the average molecular weight of the chitosan as determined by gel permeation chromatography is from about 105 to about 106.

In certain embodiments of the present invention, the oxidized cellulose and/or chitosan is complexed with collagen to form structures of the kind described in WO98/00180 and WO98/00446, the entire contents of which are expressly incorporated herein by reference. For example, the oxidized cellulose may be in the form of milled ORC fibres that are dispersed in a freeze-dried collagen sponge. This provides for certain therapeutic and synergistic effects arising from the complexation with collagen.

In particular embodiments, the substrate comprises (and may consist essentially of) a mixture of: (a) collagen and/or chitosan; and (b) oxidized regenerated cellulose, for example in a dry weight ratio range of from about 90:10 to about 10:90 of collagen/chitosan:ORC, preferably from about 75:25 to about 25:75, and particularly from about 60:40 to about 40:60.

The materials according to the present invention may be provided in the form of beads, flakes, powder, and preferably in the form of a film, a fibrous pad, a web, a woven or non-woven fabric, a freeze-dried sponge, a foam or combinations thereof. In certain embodiments, the solid bioabsorbable substrate is selected

from the group consisting of woven fabrics, knitted fabrics, and nonwoven fabrics, all of which may be made by conventional methods. In other embodiments, the solid bioabsorbable substrate may comprise (or consist essentially of) a freeze-dried sponge or a solvent-dried sponge. Methods of making freeze-dried and solvent-dried sponges are described in EP-A-1153622 and EP-A-0838491, the entire contents of which are incorporated herein by reference.

The solid bioabsorbable substrate is typically in sheet form, for example a sheet of material having an area of from about 1cm^2 to about 400cm^2, in particular from about 2cm^2 to about 100cm^2. The basis weight of the sheet is typically from about 100g/m^2 to about 5000g/m^2, for example from about 400g/m^2 to about 2000g/m^2.

The solid bioabsorbable substrate material may make up at least 50% by weight of the wound dressing material, for example at least 75% by weight or at least 90% by weight.

The term "dyestuff" refers to a material that is useful as a colorant for textile materials, that is to say an organic compound that is strongly light-absorbing in the visible region 400-700nm. In certain embodiments, the antioxidant dyestuff is selected from the group consisting of aniline dyes, acridine dyes, thionine dyes, bis-naphthalene dyes, thiazine dyes, azo dyes, anthraquinone dyes, and mixtures thereof. For example, the antioxidant dyestuff may be selected from the group consisting of gentian violet, aniline blue, methylene blue, crystal violet, acriflavine, 9-aminoacridine, acridine yellow, acridine orange, proflavin, quinacrine, brilliant green, trypan blue, trypan red, malachite green, azacrine, methyl violet, methyl orange, methyl yellow, ethyl violet, acid orange, acid yellow, acid blue, acid red, thioflavin, alphazurine, indigo blue, methylene green, and mixtures thereof.

The antioxidant dyestuff may be present in the wound dressing material according to the invention in an amount of from about 0.05% to about 5wt.%, typically about 0.2 to about 2wt.% based on the dry weight of the material.

The wound dressing material may also comprise up to 20% by weight, preferably less than 10% by weight of water. The material may also contain 0-40% by weight, preferably 0-25% by weight of a plasticiser, preferably a polyhydric alcohol such as glycerol. The material may also comprise 0-10% by weight, preferably 0-5% by weight of one or more therapeutic wound healing agents, such as non-steroidal anti-inflammatory drugs (e.g. acetaminophen), steroids, antibiotics (e.g. penicillins or streptomycins), antiseptics (e.g. silver sulfadiazine or chlorhexidine), or growth factors (e.g. fibroblast growth factor or platelet derived growth factor). All of the above percentages are on a dry weight basis.

The wound dressing material according to the present invention is preferably sterile and packaged in a microorganism-impermeable container.

Preferably, the material according to the present invention has a free radical activity, that is to say an antioxidant activity, of at least about 15% in the diphenylpicrylhydrazyl (DPPH) test, measured as percentage reduction in absorbance at 524nm after 4 hours of a 0.5%w/v dispersion of the polysaccharide in 10-4M DPPH, as described further hereinbelow in Procedure 1. Preferably the percentage reduction in absorbance in the DPPH test (after correction for any absorbance by the dye) is at least about 25%, more preferably at least about 50%, and most preferably at least about 75%.

Alternatively or additionally, the material according to the present invention may exhibit antioxidant activity as measured by its ability to inhibit the oxidation of ABTS (2,2'-azino-di-[3-ethylbenzthiazoline sulphonate]) by a peroxidase.

Preferably, the material according to the present invention will absorb water or wound fluid and hence become wet, swell or become a gelatinous mass but will not spontaneously dissolve or disperse therein. That is to say, it is hydrophilic but has a solubility of preferably less than about 1g/liter in water at 25°C. Low solubility renders such materials especially suitable for use as wound dressings to remove reactive oxygen species from the wound fluid.

The antioxidant properties of the materials according to the present invention suggest applications in a range of medical applications, including the treatment of acute surgical and traumatic wounds, burns, fistulas, venous ulcers, arterial ulcers, pressure sores (otherwise known as decubitus ulcers), diabetic ulcers, ulcers of mixed aetiology, and other chronic or necrotic wounds and inflammatory lesions and disorders. The materials according to the present invention are primarily intended for the treatment of non-infected wounds, that is to say wounds showing no clinical signs of infection, but they may also have a useful antimicrobial effect in the treatment of infected wounds.

Accordingly, in a second aspect the present invention provides the use of a material according to the present invention for the preparation of a medicament for the treatment of a wound. Preferably, the wound is a chronic wound. More preferably, the chronic wound is selected from the group consisting of ulcers of venous, arterial or mixed aetiology, decubitus ulcers, or diabetic ulcers.

In a related aspect, the present invention provides a method of treatment of a wound in a mammal comprising applying thereto a therapeutically effective amount of a material according to the present invention. Preferably, the wound is a chronic wound.

In a third aspect, the present invention provides a wound dressing comprising an antioxidant wound dressing material according to the present invention.

The wound dressing is preferably in sheet form and comprises an active layer of the material according to the invention. The active layer would normally be the wound contacting layer in use, but in some embodiments it could be separated from the wound by a liquid-permeable top sheet. Preferably, the area of the active layer is from about 1cm^2 to about 400 cm^2, more preferably from about 4cm^2 to about 100cm^2.

Preferably, the wound dressing further comprises a backing sheet extending over the active layer opposite to the wound facing side of the active layer. Preferably,

the backing sheet is larger than the active layer such that a marginal region of width 1mm to 50mm, preferably 5mm to 20mm extends around the active layer to form a so-called island dressing. In such cases, the backing sheet is preferably coated with a pressure sensitive medical grade adhesive in at least its marginal region.

Preferably, the backing sheet is substantially liquid-impermeable. The backing sheet is preferably semipermeable. That is to say, the backing sheet is preferably permeable to water vapour, but not permeable to liquid water or wound exudate. Preferably, the backing sheet is also microorganism-impermeable. Suitable continuous conformable backing sheets will preferably have a moisture vapor transmission rate (MVTR) of the backing sheet alone of 300 to 5000 g/m^2/24hrs, preferably 500 to 2000 g/m^2/24hrs at 37.5 °C at 100% to 10% relative humidity difference. The backing sheet thickness is preferably in the range of 10 to 1000 micrometers, more preferably 100 to 500 micrometers. It has been found that such moisture vapor transmission rates allow the wound under the dressing to heal under moist conditions without causing the skin surrounding the wound to macerate.

Suitable polymers for forming the backing sheet include polyurethanes and poly alkoxyalkyl acrylates and methacrylates such as those disclosed in GB-A-1280631. Preferably, the backing sheet comprises a continuous layer of a high density blocked polyurethane foam that is predominantly closed-cell. A suitable backing sheet material is the polyurethane film available under the Registered Trade Mark ESTANE 5714F.

The adhesive (where present) layer should be moisture vapor transmitting and/or patterned to allow passage of water vapor therethrough. The adhesive layer is preferably a continuous moisture vapor transmitting, pressure-sensitive adhesive layer of the type conventionally used for island-type wound dressings, for example, a pressure sensitive adhesive based on acrylate ester copolymers, polyvinyl ethyl ether and polyurethane as described for example in GB-A-1280631. The basis

weight of the adhesive layer is preferably 20 to 250 g/m^2, and more preferably 50 to 150 g/m^2. Polyurethane-based pressure sensitive adhesives are preferred.

Further layers of a multilayer absorbent article may be built up between the active layer and the protective sheet. For example, these layers may comprise an absorbent layer between the active layer and the protective sheet, especially if the dressing is for use on exuding wounds. The optional absorbent layer may be any of the layers conventionally used for absorbing wound fluids, serum or blood in the wound healing art, including gauzes, nonwoven fabrics, superabsorbents, hydrogels and mixtures thereof. Preferably, the absorbent layer comprises a layer of absorbent foam, such as an open celled hydrophilic polyurethane foam prepared in accordance with EP-A-0541391, the entire content of which is expressly incorporated herein by reference. In other embodiments, the absorbent layer may be a nonwoven fibrous web, for example a carded web of viscose staple fibers. The basis weight of the absorbent layer may be in the range of 50-500g/m^2, such as 100-400g/m^2. The uncompressed thickness of the absorbent layer may be in the range of from 0.5mm to 10mm, such as 1mm to 4mm. The free (uncompressed) liquid absorbency measured for physiological saline may be in the range of 5 to 30 g/g at 25°. Preferably, the absorbent layer or layers are substantially coextensive with the active layer.

The wound facing surface of the dressing is preferably protected by a removable cover sheet. The cover sheet is normally formed from flexible thermoplastic material. Suitable materials include polyesters and polyolefins. Preferably, the adhesive- facing surface of the cover sheet is a release surface. That is to say, a surface that is only weakly adherent to the active layer and the adhesive on the backing sheet to assist peeling of the adhesive layer from the cover sheet. For example, the cover sheet may be formed from a non-adherent plastic such as a fluoropolymer, or it may be provided with a release coating such as a silicone or fluoropolymer release coating.

Typically, the wound dressing according to the present invention is sterile and packaged in a microorganism-impermeable container.

In a fourth aspect, the present invention provides a method of manufacture of an antioxidant wound dressing material, comprising the step of dyeing a bioabsorbable substrate material with an antioxidant dye.

The method according to the present invention may be used to prepare a wound dressing according to the present invention.

The method of the present invention may comprise dyeing a substrate material in sheet form, for example a woven, nonwoven or knitted fabric or sponge sheet of the substrate material by immersing it in a dye bath, followed by washing to remove unbound dye and drying. In other embodiments, the substrate material may be dyed while it is in fibrous or particulate form, followed by forming the material into a sheet. For example, a slurry of fibers or particles of the substrate material may be treated with dye, and then freeze-dried to form a dyed sponge.

It will be appreciated that any feature or embodiment that is described herein in relation to any one aspect of the invention may also be applied to any other aspect of the invention equally.

Certain specific embodiments of the present invention will now be described further in the following examples.

Example 1

An antioxidant wound dressing material based on a collagen/ORC freeze-dried sponge material is prepared as follows.

The collagen component is prepared from bovine corium as follows. Bovine corium is split from cow hide, scraped and soaked in sodium hypochlorite solution (0.03% w/v) to inhibit microbial activity pending further processing. The corium is then washed with water and treated with a solution containing sodium hydroxide (0.2% w/v) and hydrogen peroxide (0.02% w/v) to swell and sterilize the corium at ambient temperature. The corium splits then undergo an alkali treatment step in a

solution containing sodium hydroxide, calcium hydroxide and sodium bicarbonate (0.4% w/v, 0.6% w/v and0.05% w.v, respectively) at pH greater than 12.2, ambient temperature, and for a time of 10-14 days, with tumbling, until an amide nitrogen level less than 0.24mmol/g is reached. The corium splits then undergo an acid treatment step with 1% hydrochloric acid at ambient temperature and pH 0.8-1.2. The treatment is continued with tumbling until the corium splits have absorbed sufficient acid to reach a pH less than 2.5. The splits are then washed with water until the pH value of corium splits reaches 3.0-3.4. The corium splits are then comminuted with ice in a bowl chopper first with a coarse comminution and then with a fine comminution setting. The resulting paste, which is made up in a ratio of 650g of the corium splits to 100g of water, as ice, is frozen and stored before use in the next stage of the process. However, the collagen is not freeze-dried before admixture with the ORC & other components in the next stage.

The ORC component of the freeze-dried pad is prepared as follows. A SURGICEL cloth (Johnson & Johnson Medical, Arlington) is milled using a rotary knife cutter through a screen-plate, maintaining the temperature below 60°C.

Methylene blue, an acidic dye, was incorporated by dissolving an appropriate amount of the dye in 0.05M acetic acid and adding to the collagen paste with the milled ORC powder to obtain a final solids concentration of 1%. Samples were made in which the dye was incorporated at the following concentrations in the slurry: 0% (reference example), 1mg/ml, 0.5mg/ml and 0.1mg/ml.

The resulting slurries were poured to a depth of 3mm in petri dishes, placed onto freezer shelves where the temperature has been preset to -40°C. The freeze-drier programme was then initiated to dry and dehydrothermally cross-link the collagen and ORC to form sponge pads. On completion of the cycle, the vacuum was released, sponge samples were then packaged, and sterilized by cobalt 60 gamma-irradiation.

Example 2

The procedure of Example 1 was followed, but replacing the methylene blue dye by crystal violet, a basic dye. The crystal violet was incorporated at the following concentrations in the slurry: 0% (reference example), 1mg/ml, 0.5mg/ml and 0.1mg/ml.

Example 3

The procedure of Example 1 was followed, but replacing the methylene blue dye by flavin 3,6-Diaminoacridine hemisulfate, a basic dye. The flavin was incorporated at the following concentrations in the slurry: 0% (reference example), 1mg/ml, 0.5mg/ml and 0.1mg/ml.

Example 4

The procedure of Example 1 was followed, but replacing the methylene blue dye by flavin 3,6-Diaminoacridine hemisulfate, a basic dye. The flavin was incorporated at the following concentrations in the slurry: 0% (reference example), 1mg/ml, 0.5mg/ml and 0.1mg/ml.

Example 5

The procedure of Example 1 was followed, but replacing the methylene blue dye by a mixture of methylene blue and flavin 3,6-Diaminoacridine hemisulfate, each dye being incorporated in the slurry at a concentration of 0.5mg/ml.

Example 6

The procedure of Example 1 was followed, but replacing the methylene blue dye by a mixture of crystal violet and flavin 3,6-Diaminoacridine hemisulfate, each dye being incorporated in the slurry at a concentration of 0.5mg/ml.

Example 7

The procedure of Example 1 was followed, but replacing the methylene blue dye by a mixture of crystal violet and methylene blue, each dye being incorporated in the slurry at a concentration of 0.5mg/ml.

The sponges according to the invention obtained in Examples 1 to 7 all showed stable absorption of the dyes. The sponges could be been soaked in serum at 25°C for a number of days and remained coloured at all times. Depending on concentration of dye added there was an initial release of the excess dye and then a gradual release as the sponges began to degrade.

Procedure 1

The ability of the wound dressing materials to react with and remove oxygen containing free radicals is assessed by the DPPH test described in WO94/13333, the entire content of which is expressly incorporated herein by reference. The test is adapted from that described by Blois M.S. in Nature 181: 1199 (1958), and Banda P.W. et al., in Analytical Letters 7: 41 (1974).

Briefly, the wound dressing material under test (2.5mg; 5mg; & 25mg sample sizes) was suspended in 2.5ml of 0.1M pH 7.0 phosphate buffer. A solution of diphenylpicrylhydrazyl (DPPH) in methanol (10-4 M) was added in an amount of 2.5 ml and the mixture was shaken and stored in the dark at 20°C. The samples were assessed by measurement of their light absorbance at 524nm over 6 hours in comparison with a control, particular attention being paid to the figure after 4 hours. The percentage reduction of absorbance relative to the control after 4 hours gives the DPPH test value, with a reproducibility generally of ±5%. This value may conveniently be expressed in terms of a simple reduction in absorbance units (AU) relative to the control as shown in Figure 2 in which the DPPH control solution containing no test sample produced an absorbance reading of 0.506 AU.

Ascorbic acid, a well known antioxidant, provides a useful positive control substance for comparative purposes. Freeze-dried sponges of chitin/chitosan and hydroxyethyl cellulose were used as negative controls.

Application of this test to the materials according to the present invention of Examples 1-7 resulted in DPPH test values of 80 - 90% for the positive control (10-4M). In contrast, the negative controls chitin/chitosan and hydroxyethyl cellulose exhibited much lower DPPH values of less than 15%. The collagen/ORC

without any added dye exhibited some activity in the DPPH test, indicating that ORC itself has some antioxidant properties. The dyed materials according to the present invention exhibited significantly higher activity in the DPPH test than collagen/ORC alone, consistent with antioxidant activity of the dyes.

The above embodiments have been described by way of example only. Many other embodiments falling within the scope of the accompanying claims will be apparent to the skilled reader.

CLAIMS

1. A wound dressing material comprising a solid bioabsorbable substrate dyed with an antioxidant dyestuff.

2. A wound dressing material according to claim 1, wherein the substrate comprises a solid bioabsorbable material selected from the group consisting of collagens, oxidized celluloses, alginates, chitosans, galactomannans, glycosaminoglycans, and mixtures thereo

3. A wound dressing material according to claim 2, wherein the substrate comprises a solid bioabsorbable material selected from the group consisting of collagens, oxidized regenerated celluloses, alginates, and mixtures thereof.

4. A wound dressing material according to any preceding claim, wherein the solid bioabsorbable substrate is selected from the group consisting of woven fabrics, knitted fabrics, nonwoven fabrics, freeze-dried sponges, solvent-dried sponges and combinations thereof.

5. A wound dressing material according to any preceding claim, wherein the antioxidant dyestuff is selected from the group consisting of aniline dyes, acridine dyes, thionine dyes, bis-naphthalene dyes, thiazine dyes, azo dyes, anthraquinones, and mixtures thereof.

6. A wound dressing material according to any preceding claim, wherein the antioxidant dyestuff is selected from the group consisting of gentian violet, aniline blue, methylene blue, crystal violet, acriflavine, 9-aminoacridine, acridine yellow, acridine orange, proflavin, quinacrine, brilliant green, trypan blue, trypan red, malachite green, azacrine, methyl violet, methyl orange, methyl yellow, ethyl violet, acid orange, acid yellow, acid blue, acid red, thioflavin, alphazurine, indigo blue, methylene green, and mixtures thereof.

7. A wound dressing material according to any preceding claim, wherein the antioxidant dyestuff is present in an amount of from about 0.2 to about 2wt.% based on the dry weight of the material.

8. A wound dressing material according to any preceding claim, wherein the material is in sheet form.

9. A wound dressing material according to any preceding claim, wherein the material is sterile and packaged in a microorganism-impermeable container.

10. A wound dressing material according to any preceding claim, wherein the material has a free radical activity in the diphenylpicrylhydrazyl (DPPH) test for antioxidant activity as herein defined of at least about 15%.

11. Use of a material according to any one of claims 1 to 10 for the preparation of a medicament for the treatment of a wound.

12. Use according to claim 11, wherein the wound is a chronic wound, preferably selected from the group consisting of ulcers of venous ulcers, decubitus ulcers, or diabetic ulcers.

13. A method of manufacture of an antioxidant wound dressing material, comprising the step of dyeing a bioabsorbable substrate material with an antioxidant dye.

14. A method according to claim 13 for the manufacture of a wound dressing material according to any of claims 1 to 10.

15. A wound dressing comprising an antioxidant wound dressing material according to any of claims 1 to 10.

16. A wound dressing according to claim 15, wherein the material is sterile and packaged in a microorganism-impermeable container.

ABSTRACT

ANTIOXIDANT WOUND DRESSING MATERIALS

A wound dressing material comprising a solid bioabsorbable substrate dyed with an antioxidant dyestuff. The substrate may comprise collagen or oxidized regenerated cellulose, and the dyestuff may for example be an aniline or acridine dye. Also provided are methods of making such materials, and wound dressings comprising such materials.

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